EXHIBIT F

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CASE STUDY

Modafinil for the treatment of diminished responsiveness in a patient recovering from brain surgery

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Abstract

Primary objective: This case report reviews the history and post-operative status of a 77-year-old woman who underwent transcallosal resection of an intra-ventricular haemorrhagic subependymoma and who remained in a deep post-operative state of lethargy and listlessness.

Main outcome measures: Glasgow Coma Scale (GCS) and detailed clinical observations.

Results: The patient ($GCS = 8$) was initiated on methylphenidate 20 mg per day on the 6th day after surgery, but treatment was discontinued 2 days later due to elevated blood pressure and persistent tachycardia. Pemoline 37.5 mg per day was initiated, but treatment was stopped after 3 days due to lack of response. Treatment with modafinil 400 mg per day was initiated on the 11th day after surgery and the patient's consciousness level rapidly improved on the 14th day. On the 16th day after surgery, she was completely alert ($GCS = 15$).

Conclusions: Modafinil appeared to be beneficial for improving wakefulness and responsiveness in a patient with central nervous system trauma in the post-operative state.

Keywords: *Modafinil, Glasgow coma scale, level of consciousness, brain surgery*

Introduction

Modafinil, a wake-promoting agent, is effective for treating excessive daytime sleepiness associated with narcolepsy [1]. Its mechanism of action differs from that of stimulants, which have broad effects within the brain. The wake-promoting effect of modafinil appears to be the result of selective modulation of the hypothalamocortical pathways involved in the regulation of normal wakefulness [2]. Modafinil also has been shown to decrease fatigue related to multiple sclerosis [3] and to counteract the debilitating effects of sleep deprivation on fatigue, mood and cognition [4].

Treatment of patients with traumatic brain injury (TBI) and other types of trauma to the central nervous system (CNS) has traditionally been limited to physical and occupational therapy, lifestyle modifications and other supportive measures. Treatment with stimulants, such as methylphenidate or dextroamphetamine, has also been used with mixed results to improve arousal status and facilitate recovery of consciousness and responsiveness [5]. This study reports the case of a patient who underwent transcallosal resection of an intra-ventricular haemorrhagic subependymoma and experienced a profound post-operative decrease in responsiveness to the environment and external stimuli, which did not improve after treatment with stimulants but resolved after the initiation of modafinil.

Case report

A 77-year-old woman was in excellent health until she reported fainting during an airline flight. Magnetic resonance imaging (MRI) revealed that the patient had a small intra-ventricular tumour. Because there was no indication of a pressure effect, hydrocephalus or adverse neurological sequelae,

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immediate surgical intervention was not considered to be warranted. The patient's medical condition was routinely monitored at follow-up visits.

Three years after the tumour was initially detected, the patient suddenly developed severe headaches and experienced episodes of confusion, disorientation and drowsiness. She also reported impairments in recent memory and immediate recall. There was evidence of a large haematoma and ventriculomegaly. Axial computed tomography (CT) and MRI scans of the brain showed that the tumour had increased in size but had not invaded the basal ganglia or surrounding extra-ventricular area. Transcallosal surgery (including perforation of the third ventricle) was performed and a haemorrhagic subependymoma, including the necrotic centre, was partially resected along with several paramedian veins to prevent further haemorrhaging. During the post-operative period, haemodynamic function recovered fully. However, the patient remained in a deep state of lethargy and listlessness, although she was able to open her eyes and withdraw her arms in response to noxious stimuli. The patient's speech was also incomprehensible and she had a Glasgow Coma Scale (GCS) score of 8.

Although serial head scans failed to show evidence of brain oedema, obstructive hydrocephalus or other complications, the patient's condition persisted. The initial haemorrhagic lesion appeared stable in size after surgery. Treatment with stimulants was initiated. On the 6th day after surgery, a trial with methylphenidate was initiated at a dosage of 10 mg twice daily administered by nasogastric tube (NGT). Elevated blood pressure and persistent tachycardia developed on the 8th day after surgery after the 4th dose of methylphenidate; therefore, this treatment was abandoned. Vital signs improved after discontinuation of methylphenidate. Even though, theoretically, higher doses might have been effective, they were considered relatively contraindicated in view of the undesirable effects that developed. Pemoline was then started at 37.5 mg daily by NGT, but treatment was stopped after 3 days because there was no rapid, discernable improvement in the patient's condition. Degree of responsiveness continued to be unchanged (GCS = 8).

On the 11th day after surgery, treatment with modafinil 200 mg twice daily (7 am and 7 pm) was initiated by NGT. The patient's level of consciousness improved rapidly on the 3rd day of modafinil administration (GCS = 10). In the subsequent 3 days, the patient became increasingly alert and started to communicate; her GCS score improved to 14. The NGT was removed because the patient was able to feed herself. The next day, she was able to take a few steps with assistance. By the time she was transferred to the rehabilitation unit on the 16th day after surgery, she was completely alert (GCS = 15). This improvement was attributed to modafinil because additional brain structural injury or haemorrhage had been ruled out and the original area of haemorrhage had remained static after surgery. Modafinil was decreased to 200 mg once daily (7 am) 1 week later and was discontinued after 1 month. Adverse cardiovascular effects were not observed at any time while the patient was receiving modafinil. Follow-up CT scans performed after discontinuation of modafinil therapy at 6 and 12 weeks disclosed gradual resolution of the intra-ventricular haemorrhage. Except for persistent recent-memory dysfunction, the patient made an otherwise complete recovery and returned to her usual daily routines.

Discussion

The rapid and marked improvements in alertness and responsiveness in this patient following the initiation of treatment with modafinil are consistent with those observed in a case series study [6] of 10 patients with TBI and two patients with somnolence due to sedating psychiatric drugs. Administration of modafinil in the 12 patients either replaced a Schedule II agent or was used initially for excessive daytime sleepiness [6]. Treatment with modafinil 100–400 mg per day taken once every morning resulted in moderate-to-marked improvements in daytime wakefulness in all patients [6].

In the present case report, the patient became listless and lethargic following partial resection of a large subependymoma. The anatomical systems involved in consciousness are rather complex; however, in this patient's case, her markedly impaired level of consciousness was probably related to CNS structures affected by the tumour, tumour-related haemorrhaging and the subsequent surgery. Rapidly enlarging intra-ventricular haemorrhage, mechanical and vascular involvement of the periventricular gray matter surrounding the third ventricle (which was surgically penetrated) and interruption of some of the hypothalamocortical pathways ascending through that area probably contributed to her altered state of consciousness. Following initiation of treatment with modafinil, the patient demonstrated a rapid and pronounced improvement in her medical condition. This response is particularly noteworthy given that the patient did not respond favourably to treatment with two commonly used stimulants.

The decision to initiate the patient on a twice-daily dose of modafinil was made empirically, with support from the results of a recent study [7] in which twice-daily dosing of modafinil was found to have significantly improved arousal effects over once-daily dosing in patients with narcolepsy who were exceptionally sleepy later in the day. These clinical observations suggest that modafinil may be useful for improving wakefulness and responsiveness in patients with CNS trauma in the post-operative state. Modafinil may also reduce some of the adverse sequelae that can occur as a result of surgical interventions to address underlying CNS pathologies. The surgical nature of this case produced a very localized involvement of certain CNS structures. Other types of brain injury resulting in diminished responsiveness will require adequate clinical trials to evaluate whether the use of modafinil is warranted under those circumstances.

References

1. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000; 54:1166–75.
2. Scammell TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, Miller MS, Saper CB. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. Journal of Neuroscience 2000;20:8620–8.
3. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. Journal of Neurology, Neurosurgery and Psychiatry 2002;72:179–83.
4. Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, Thompson M, Mack II. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. Journal of Sleep Research 1995;4:212–28.
5. Kraus MF. Neuropsychiatric sequelae of stroke and traumatic brain injury: the role of psychostimulants. International Journal of Psychiatry in Medicine 1995;25:39–51.
6. Teitelman E. Off-label uses of modafinil. American Journal of Psychiatry 2001;158:1341.
7. Schwartz JR, Feldman NT, Bogan RK. Dosing-regimen effects of modafinil for improving daytime wakefulness in patients with narcolepsy. Clinical Neuropharmacology 2003; 26:252–7.